REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office Action dated October 1, 2008 are respectfully requested.

I. Summary of Examiner Interview

Applicants thank Examiner Riggs Applicants for granting Applicants a telephonic interview on February 19, 2009. Compliant with M.P.E.P. § 713.04, Applicants provide the following summary of the interview. The 101, 112 and 103 rejections set forth in the October 1, 2008 Office Action and proposed claim amendments were discussed.

II. Status of the Claims

Claims 15-21 are pending in the application.

With this amendment, claim 15 is amended.

III. Amendments to the Claims

Independent claim 15 is amended for clarity and recites wherein each module is an exon or an intron and has a length. Recitation of "subsequence" is replaced with the term "module." Support for this amendment can be found, for example, in paragraph [0037] of page 6 of the specification as originally filed.

Claim 15 is further amended to recite that the representation indicates the relative expression levels of the plurality of splice variants of the gene. Support for this amendment can be found, for example, in claim 1 as originally filed and throughout the specification.

Claim 15 is further amended to recite an output device that is linked to a suitably programmed computer. Support for this amendment can be found, for example, in paragraph [0078] on page 16 of the specification as originally filed.

No new matter has been added by these amendments

IV. Rejection Under 35 U.S.C. § 101

Claims 15-21 were rejected under 35 U.S.C. § 101. The Examiner alleges that the claims are directed to non-statutory subject matter. Applicants respectfully traverse the rejection for the following reason, and in view of the amendment to claim 15.

Claim 15 recites that a relative expression level for each splice variant is determined using a mathematical algorithm to expression level data obtained using exon-exon junction indicator polynucleotides that selectively hybridize to exon-exon junctions of a given splice variant. In other words, the method of claim 15 requires that indicator polynucleotides are used

in a manner such that they selectively hybridize to exon-exon junctions of a given splice variant. This physical step of nucleic acid hybridization is subsequently "transformed" into expression data, which is then used in a mathematical algorithm. For this reason, Applicants submit that the claim satisfies the legal standards to qualify as patentable subject matter. However, in the interest of advancing prosecution, claim 15 is additionally amended to recite an output device linked to a suitably programmed computer.

In view of the amendment, Applicants respectfully request withdrawal of the rejection.

IV. Rejections Under 35 U.S.C. § 112, Second Paragraph (Indefiniteness)

Claims 15-21 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite with respect to the language "displaying a graphical representation wherein the modules of the given splice variants are aligned with corresponding modules or exons of other splice variants of the gene." The Examiner states that the limitations of phrases such as "the given splice variants" and "other splice variants" are unclear. The Examiner states that "it is unclear whether the first subsequence and second subsequence are 'the given splice variants.'"

The Examiner further states that the metes and bounds of the limitation of "modules...are aligned with corresponding modules or exons of other splice variants" are unclear.

Response

The amendments to claim 15, from which all the other rejected claim depend, are believed to address each portion of the rejection.

In particular, claim 15 has been amended to delete the term "subsequence." Further, the term "module" is defined as being an exon or an intron and having a length. As stated in the preamble of claim 15, each of the plurality of splice variant have modules. Thus, the term "module" as used in claim 15 as presently amended clearly refers to a subsequence or portion of an individual splice variant.

Claim 15 is further amended to recite that the modules are aligned to each other. Support for the phrase "aligned to each other" can be found, for example, in paragraph 36 of the specification as originally filed. Moreover, one of skill in the art readily understands that the alignment of modules to each other refers to the alignment of modules, sharing identical or similar sequences, from individual splice variants on a vertical scale as illustrated in Figures 1-5, 8, 10, 11-14, and 16-17 of the present application. For example, if a gene has five exons (exons 1-5) and three of the five splice variants contain modules representing exon 1, then an alignment of the modules (exons) refers to a vertical alignment of the three exon 1 modules. One of skill in the art would not interpret claim 15 to suggest that modules within a single splice

variant would be aligned to each other, or that a module that is an exon would be aligned with a module that is an intron. One of skill in the art would further understand the alignment of modules "to each other" inherently refers to the alignment of modules derived from the different, individual splice variants of the plurality of splice variants.

Withdrawal of the rejections is respectfully requested.

V. Rejections Under 35 U.S.C. § 103

Claims 15-21 were rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Loraine *et al.* (U.S. Pub. No. 2004/0049354).

The rejection is traversed in view of the foregoing amendments and following remarks.

A. The Present Claims

The present claims, as exemplified by independent claim 15, relate to "[a] method in a computer system for displaying a graphical representation of expression levels of a plurality of splice variants of a gene in one or more samples, each of the plurality of splice variants of the gene having modules, the method comprising:

identifying modules for each splice variant of the gene, wherein each module is an exon or an intron and has a length,

applying a first mathematical function to the length of a first module of a first splice variant to obtain a scaled length for the first module for graphical representation,

applying a second, different, mathematical function to the length of a second module of the first splice variant to obtain a scaled length for the second module for graphical representation,

determining a relative expression level for each of the plurality of splice variants by applying a mathematical algorithm to expression level data obtained using exon-exon junction indicator polynucleotides that selectively hybridize to exon-exon junctions of the plurality of splice variants, and

displaying a graphical representation wherein the modules of the given splice variants are aligned with corresponding modules or exons of other splice variants of the gene, wherein the representation indicates the relative expression levels of the modules, and wherein the scaled length of the first subsequence and the scaled length of the second subsequence are displayed simultaneously.

B. Summary of the Cited Art

Loraine *et al.* (U.S. Pub. No. 2004/0049354) describe computer implemented methods for analyzing splice variant data received by an input manager. The methods appear to tie known functional and experimental information to data obtained using probe sets (*e.g.*, ¶ [0006]).

C. Analysis

To establish a *prima facie* case of obviousness, three basic criteria must be met. The third criterion is that the prior art references (or references when combined) must teach or suggest all the claim limitations. Applicants submit that a *prima facie* case of obviousness has not been established for at least the following reasons.

C1. Loraine *et al.* do not show or suggest the application of two different mathematical functions to two different modules in a single splice variant.

Claim 15 is directed, in part, to applying at least two different mathematical functions to the lengths of two different modules within a single splice variant. In contrast, Loraine *et al.* teach the display of alternative splice variants aligned to a scale (see paragraph [0137]). Loraine *et al.* further teach a variety of scales that may vary in units and magnitude including linear, logarithmic, and other types of scales. However, Loraine *et al.* do not teach application of the "variety" of scales to a single alignment.

The Examiner points to the statement in Loraine *et al.* that "it will be understood that many other graphical arrangements or devices known to those of skill in the art may be used to distinguish splice variants and/or distinguish exons belonging to one or more splice variants." Applicants submit, however, that such a statement is generic in nature and provides no guidance that would lead one of skill in the art to apply two different mathematical functions to two different modules in a single splice variant. Examples of methods to distinguish exons belonging to one or more splice variants include color-coding, different shaped objects, different arrangement. Such methods of depicting sequence substructures are well-known in the art. What was not known at the time of filing was the method of applying to different scales to two different lengths within a single splice variant.

In paragraph [0139], Loraine *et al.* discuss that the base-counting reference (1205 in Figure 12) may display a scale that may include a range of bases or other reference points determining the scale of reference may be user selectable so that, for example, bases may be counted from the beginning of a gene of interest chosen by the user. In such a display, one of

skill in the art would not represent the lengths of two or more subsequences using multiple scales. Rather, the user may choose to display portions of a splice variant, on a single scale. Therefore, this passage in Loraine et al. also fails to show or suggest the claimed feature of applying two different mathematical functions to two different modules in a single splice variant

C2. Loraine *et al.* do not teach representation of relative expression levels of individual splice variants.

Claim 15 as presently amended is directed, in part, to determining and displaying relative expression levels of each of the plurality of splice variants of the gene. More specifically, the claimed method comprises displaying a graphical representation of expression levels of a plurality of splice variants of a gene, wherein the relative expression level for each splice variant is determined by applying a mathematical algorithm to expression level data obtained using an oligonucleotide array in which exon-exon junction indicator polynucleotides that selectively hybridize to exon-exon junctions of a given splice variant are used as probes.

Loraine *et al.* disclose in paragraph [0144] and elsewhere in the specification that the relative abundance of alternative splice variants may be displayed in GUI. However, this expression level display taught by Loraine *et al.* represents sums of module, or exon, expression. As stated by the Examiner at the top of page 4 of the Office Action mailed July 6, 2007, Loraine *et al.* teach the relative expression level of the exon in the alternative splice transcripts, wherein various bar heights may occur within each exon and between different exons. As an example, Figure 12 of Loraine *et al.*, shows that the height of exon bar 1265 may correspond to the frequency with which an exon, or partial exon, occurs in the alternative splice transcripts (paragraph [0144]). Clearly such display was obtained by measuring, for example, the hybridization signal from each of the exon probes designed to measure expression of a particular gene. The hybridization signal level is therefore a measurement of hybridization of each exon probe to all splice variants which comprise that particular exon.

Therefore, Loraine *et al.* do not teach or suggest a method of determining relative expression levels of individual and distinct splice variants generated by the gene of interest as presently claimed.

More specifically, Loraine *et al.* do not disclose application of a mathematical algorithm to expression level data to determine the relative expression levels of each of a plurality of splice variants. In the absence of the present disclosure, one of ordinary skill in the art could not take the teachings of Loraine et al. to devise a method for displaying a graphical representation of expression levels of a plurality of splice variants, wherein the representation indicates the expression levels of each of the plurality of splice variants of the gene.

Since the Loraine *et al.* do not teach the above elements of independent claim 15, from which the other rejected claims depend, the pending claims are not obvious in view of the cited reference.

Applicants respectfully request withdrawal of the rejection.

VI. Conclusion

Applicants believe the foregoing amendments and remarks fully address all outstanding rejection and place the application in condition for allowance. Early notice to that effect is earnestly requested. If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to call the undersigned at (650) 590-1919.

Respectfully submitted,

Date: March 2 2009

/Susan L. Harlocker/
Susan L. Harlocker
Registration No. 59,144

Correspondence Address:
Customer No. 79975